The Effect of the Endoscopic Duodenal-Jejunal Bypass Liner on Obesity and Type 2 Diabetes Mellitus, a Multicenter Randomized Controlled Trial

Parviez Koehestanie, MD,∗ Charlotte de Jonge, MD,†‡ Frits J. Berends, MD, PhD,* Ignace M. Janssen, MD,* Nicole D. Bouvy, MD, PhD,† and Jan Willem M. Greve, MD, PhD‡

Objectives: Investigate the safety and efficacy of 6 months’ duodenal-jejunal bypass liner (DJBL) treatment in comparison with dietary intervention for obesity and type 2 diabetes mellitus (T2DM).

Background: The DJBL is a bariatric procedure involving an impermeable sleeve that is delivered endoscopically in the proximal intestine. This procedure not only is less invasive than conventional surgical techniques but also has beneficial effects on obesity and T2DM.

Methods: A multicenter randomized controlled trial was conducted. Seventy-seven patients with obesity and T2DM were included. Thirty-eight patients were randomized to 6 months’ DJBL treatment in combination with dietary intervention (34 successfully implanted, 31 completed the study), 39 patients received only dietary intervention (controls, 35 completed the study). Total study duration for both groups was 12 months, including 6 months of post-DJBL removal follow-up.

Results: After 6 months, just before DJBL removal, the DJBL group had lost 32.0% [22.0%–46.7%] of their excess weight versus 16.4% [4.1%–34.6%] in the control group (P < 0.05). Glycated hemoglobin A1c levels improved to 7.0% [6.4%–7.5%] in the DJBL group and to 7.9% [6.6%–8.3%] in the control group (P < 0.05). In addition, 85.3% of DJBL patients showed decreased postprandial glucose excursions versus 48.7% of control patients (P < 0.05). At 12 months, excess weight loss of the DJBL group was 19.8% [10.6%–45.0%] versus 11.7% [1.4%–25.4%] in the control group (P < 0.05). HbA1c was 7.3% [6.6%–8.0%] versus 8.0% [6.8%–8.8%], DJBL versus control respectively (P = ns).

Conclusions: The DJBL is a safe and effective alternative to invasive bariatric procedures. Six months of DJBL treatment combined with diet leads to superior weight loss and improvement of T2DM when compared with diet alone.

Keywords: bariatric surgery, cardiovascular risk profile, type 2 diabetes, obesity, weight loss

From the ∗Department of General Surgery, Rijnstate Hospital, Arnhem, The Netherlands; †Department of General Surgery and NUTRIM School for Nutrition, Toxicology and Metabolism Research, Maastricht University Medical Center, Maastricht, The Netherlands; ‡Department of General Surgery, Atrium Medical Center Parkstad, Heerlen, The Netherlands. Disclosure: Supported by GI Dynamics, Inc (Lexington, MA). All data were collected under the supervision of MedPass (MedPass International, Paris, France). P. Koehestanie, N. D. Bouvy, I. M. Janssen, and J. W. M. Greve disclose the following financial relationships relevant to this publication: P. Koehestanie received consultancy fees from GI Dynamics, Inc; N. D. Bouvy and I. M. C. Janssen received an open research grant from GI Dynamics, Inc; and J. W. M. Greve received an open research grant, consultancy fees, and support for travel to meetings for the study or other purposes from GI Dynamics, Inc. C. de Jonge has no conflicts of interest relevant to this article.

Clinicaltrials.gov number: NCT00985114

Reprints: Jan Willem M. Greve, MD, PhD. Department of General Surgery, Atrium Medical Center Parkstad, PO Box 4446, 6401 CX Heerlen, The Netherlands. E-mail: j.greve@atriummcr.nl.

Copyright © 2014 by Lippincott Williams & Wilkins

ISSN: 0003-4922/14/26006-0984
DOI: 10.1097/SLA.0000000000000794

Annals of Surgery • Volume 260, Number 6, December 2014

Obesity is a rapidly growing problem worldwide. Once considered only a problem in Western society, obesity rates are now also rising dramatically in formerly developing countries. Importantly, obesity is a major risk factor for several chronic diseases, including type 2 diabetes mellitus (T2DM) and cardiovascular diseases. Furthermore, it is associated with impaired health-related quality of life. Today, more than 500 million adults are overweight and millions of these people face the dual challenge of managing T2DM and obesity. Lifestyle changes resulting in weight loss improve T2DM and are, next to medication, the most important treatment modality for T2DM. Although conservative therapy is usually successful in weight control in the short term, long-term results are often disappointing. Bariatric surgery, on the contrary, has proven its effectiveness in achieving and maintaining weight loss and improving T2DM, quality of life, and survival. Surgery is increasingly performed and effective; however, it is associated with potentially important complications and, although rare, mortality. Therefore, less invasive and safer techniques that will offer treatment of a broader spectrum of patients are searched for.

Recently, a novel nonsurgical bariatric technique has been developed, the duodenal-jejunal bypass liner (DJBL; GI Dynamics, Inc, Lexington, MA). The DJBL consists of a 60-cm long fluoropolymer liner that is delivered into and retrieved from the duodenum endoscopically. Its principle is based on the effectiveness of surgical duodenal-jejunal exclusion in treating obesity and T2DM; once placed in the duodenum, it mimics the intestinal bypass component of the well-known Roux-en-Y gastric bypass and surgical duodenal-jejunal exclusion. Clinical experience to date has demonstrated the safety of the DJBL and its ability to rapidly improve blood glucose control and induce weight loss. In addition, the DJBL has been shown to improve other metabolic parameters, including lipid profile and blood pressure.

In the current randomized controlled study, we aimed to investigate the safety of 6 months’ DJBL treatment and the effect on obesity, T2DM, and cardiovascular risk profile in obese patients with T2DM. After DJBL treatment, patients were followed up for 6 months to evaluate postremoval effects.

METHODS

Patients

Patients were considered eligible if they were between 18 and 65 years of age; had a body mass index (BMI) between 30 and 50 kg/m²; and had T2DM for less than 10 years with a glycaated hemoglobin A1c (HbA1c) level between 7.5% and 10.0%. Patients were allowed to take metformin, sulfonylurea (SU) derivates, and/or insulin with a maximum dose of 150 IU per day. Exclusion criteria were as follows: weight loss of more than 4.5 kg within 12 weeks before screening; pregnancy or intention to become pregnant; use of nonsteroidal anti-inflammatory drugs, anticoagulation therapy, corticosteroids, weight loss medication, or drugs known to affect gastrointestinal (GI) motility; substance abuse; active Helicobacter
pylori infection; probable insulin production failure as indicated by a C-peptide level of less than 1.0 ng/mL; iron deficiency or iron deficiency anemia; GI tract abnormalities or previous surgery in the GI tract that could affect the ability to place the device; symptomatic gallstones or kidney stones; known infection; bleeding disorders; gastroesophageal reflux disorder; connective tissue disorders; and severe liver or kidney failure as indicated by a creatinine level of more than 180 mmol/L.

Study Protocol

In a prospective, randomized, controlled, multicenter study, 77 patients were included in Rijnstate Hospital, Arnhem; Maastricht University Medical Center, Maastricht; and Atrium Medical Centrum Parkstad, Heerlen. As shown in Figure 1, a total of 38 patients were randomized to the DJBL treatment group and 39 patients were randomized to the control group. Patients in the DJBL group were to be treated for 6 months with the DJBL and were followed up for an additional 6 months after removal of the device. Of the DJBL group, 34 patients received implants (3 failures, 1 withdrawal). Groups were comparable with respect to age, sex, BMI, and comorbidities (Table 1).

At the initiation of the study, data on patient demographics, physical examination (including weight, BMI, and blood pressure), and medical history were collected. Electrocardiogram, chest radiograph, and abdominal ultrasonogram were obtained to rule out the presence of apparent pulmonary, cardiovascular, or GI disease. Laboratory parameters were obtained before the start of the treatment (HbA1c, fasting glucose and insulin, total cholesterol, high-density lipoprotein cholesterol, and C-peptide), and a 4-hour standard meal tolerance test was performed using a standard liquid meal (Ensure Plus vanilla flavor, Abbott Laboratories, Abbott Park, IL; 333 mL, 500 kcal, 20.8 g of protein, 67.3 g of carbohydrates, and 16.4 g of fat). During the study, all patients were prescribed a diet with a maximum of 1200 kcal for women and 1500 kcal for men, which was liquid for the first week. In addition, patients were advised to increase their physical activities. Medical treatment of T2DM was managed by a diabetes nurse under supervision of an endocrinologist.

To avoid hypoglycemic events, the dose of glucose-lowering medication, except for metformin, was reduced by 50% at the time of implant or initiation of the diet. If hypoglycemic or hyperglycemic episodes were experienced, additional adaptations to the medical treatment were performed as regular. In addition, DJBL patients were prophylactically prescribed a proton pump inhibitor for the duration of DJBL treatment to prevent peptic ulcer formation in the stomach and the duodenum.

Regular follow-up visits were carried out at 1 week, 1 month, 2 months, 3 months, 4 months, 5 months, 6 months, 7 months, 8 months, 9 months, and at 12 months. DJBL patients had an additional hospital visit 1 week after removal of the device. During these visits, weight and blood pressure were measured, adverse events were assessed, nutritional and diabetes counseling was performed, and blood was withdrawn to determine the same laboratory parameters as determined at the start of the study. The percentage of excess weight loss was calculated as follows: (Initial weight − Current weight)/Weight corresponding with BMI of 25 kg/m². In addition, a standard 4-hour meal tolerance test was performed at 1 week and at 1, 3, and 6 months in both groups.

The study was conducted in accordance with the Standard ISO 14155: 2003 on clinical investigations with medical devices and the recommendations guiding physicians in biomedical research involving human patients adopted by the 18th World Medical Assembly, Helsinki, Finland, 1964 and later revisions. The study was approved by the medical ethical committee of all 3 participating hospitals. Before the start of the study, written informed consent was obtained from all patients.

DJBL Procedure

The DJBL is a single-use endoscopic device mimicking the intestinal bypass component of the Roux-en-Y gastric bypass (Figs. 2A, B). The device consist of a 60-cm long impermeable fluoropolymer liner and a nitinol anchor, which is used to reversibly affix the device to the duodenum (Figs. 2C, D). The anchor is located in the duodenal bulb, and the liner stretches out through the duodenum and the proximal part of the jejunum. To allow food passage, the DJBL is open at both the proximal and the distal end. As a result, chyme passes through the interior of the DJBL whereas pancreatic enzymes and bile pass on the outside of the liner. Digestion and absorption of nutrients therefore start at the end of the liner, creating a bypass of the proximal intestinal tract.

Implantation of the DJBL was performed under general anesthesia with endotracheal intubation. Initial access to the stomach and the duodenum was achieved by standard gastroduodenoscopy. Next, a guide wire was advanced into the duodenum and the encapsulated device was tracked over the guide wire into the duodenum. The capsule at the distal end holds the liner and the anchor. The catheter has an atraumatic ball at the end, which is advanced through the intestine deploying the liner behind it. After full extension of the liner, the anchor was deployed in the duodenal bulb, approximately 0.5 cm distal to the pylorus. Endoscopic and fluoroscopic guidance was used to verify the correct position of the DJBL. Mean procedure time was 32 ± 4 minutes. After 6 months, the DJBL was removed as previously described. Seventeen removals were performed under general anesthesia.
anesthesia and 17 under conscious sedation. The mean procedure time of the removals was 11 ± 2 minutes.

Statistical Analysis

With a population of 35 subjects per group, a Fisher exact test using a 2-tailed or of 0.05 will have 80% power to achieve statistical significance between subject proportions of 25% (control) and 60% (device) achieving a 0.5% or more reduction in HbA1c levels at month 12. The significance between subject proportions of 25% (control) and 60% (device) achieving a 0.5% or more reduction in HbA1c levels at month 12.

The percent total weight loss was greater in the DJBL group:

\[
\text{Percent total weight loss} = \left( \frac{\text{Weight at baseline} - \text{Weight at end of study}}{\text{Weight at baseline}} \right) \times 100
\]

The percent total weight loss was 5.8% [3.2%–11.1%] in the DJBL group versus 3.5% [0.6%–8.6%] in the control group (P < 0.05).

RESULTS

DJBL Versus Control: Effect on Weight

Baseline characteristics of both groups are shown in Table 1. At baseline, the mean body weight of the DJBL group was 105.4 [98.2–116.1] kg versus 110.8 [99.7–129.0] kg in the control group (P = 0.29). Mean BMI was 34.6 [32.4–38.1] kg/m² in the DJBL group at baseline versus 36.8 [32.6–42.0] kg/m² in the control group (P = 0.16).

After 6 months, body weight had decreased by 10.6 [7.4–12.6] kg in the DJBL group (Fig. 3A). In comparison, the weight of the control group had decreased by 5.3 [1.9–10.6] kg (DJBL vs control; P < 0.05). Correspondingly, BMI decreased by 3.3 [2.2–4.2] kg/m² in the DJBL group versus 1.8 [0.7–3.4] kg/m² in the control group (Fig. 3B; P < 0.05). In addition, excess weight loss was superior in the DJBL group; 32.0% [22.0%–46.7%] in the DJBL versus 16.4% [4.1%–34.6%] in the control group, respectively (Fig. 3C; P < 0.05). Similarly, the percent total weight loss was greater in the DJBL group:

\[
\text{Percent total weight loss} = \left( \frac{\text{Weight at baseline} - \text{Weight at end of study}}{\text{Weight at baseline}} \right) \times 100
\]

The percent total weight loss was 5.3 [1.9–7.9%] vs 8.0 [4.7%–11.1%] in the DJBL group versus 5.0 [3.7] kg/m² in the control group, respectively (Table 1). mean BMI was 34.6 [32.4–38.1] kg/m² in the DJBL group versus 36.8 [32.6–42.0] kg/m² in the control group (P = 0.16). Similarly, the percent total weight loss was 8.3 [7.7–9.0%] vs 11.0 [9.3–13.1%] in the DJBL group versus 5.0 [3.7] kg/m² in the control group, respectively (Table 1). mean BMI was 34.6 [32.4–38.1] kg/m² in the DJBL group versus 36.8 [32.6–42.0] kg/m² in the control group (P = 0.16).

TABLE 1. Patient Characteristics

<table>
<thead>
<tr>
<th>Device Group (n = 34)</th>
<th>Diet Group (n = 39)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (male, no. patients)</td>
<td>21 (61.8)</td>
<td>25 (64.1)</td>
</tr>
<tr>
<td>Age, yr</td>
<td>49.5 [42–58]</td>
<td>49.0 [44–55]</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>105.4 [98.2–116.1]</td>
<td>110.8 [99.7–129.0]</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>34.6 [32.4–38.1]</td>
<td>36.8 [32.6–42.0]</td>
</tr>
<tr>
<td>HbA1c, %</td>
<td>8.3 [7.7–9.0]</td>
<td>8.3 [7.7–9.0]</td>
</tr>
<tr>
<td>Fasting glucose, mmol/L</td>
<td>11.0 [9.4–13.0]</td>
<td>11.0 [9.3–13.1]</td>
</tr>
<tr>
<td>Fasting insulin, mU/L</td>
<td>15.0 [9.0–21.0]</td>
<td>17.0 [13.0–36.0]</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>147 [139–156]</td>
<td>152 [138–160]</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>92 [82–96]</td>
<td>90 [82–96]</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>4.4 [3.9–5.0]</td>
<td>4.4 [3.6–5.3]</td>
</tr>
<tr>
<td>HDL, mmol/L</td>
<td>1.1 [0.9–1.4]</td>
<td>1.2 [0.9–1.3]</td>
</tr>
<tr>
<td>LDL, mmol/L</td>
<td>2.3 [1.9–3.1]</td>
<td>2.4 [1.8–3.0]</td>
</tr>
<tr>
<td>Triglycerides, mmol/L</td>
<td>1.7 [1.3–3.3]</td>
<td>2.0 [1.4–3.0]</td>
</tr>
</tbody>
</table>

The values are given as number (percentage) of patients or mean [interquartile range]. HDL indicates high-density lipoprotein; LDL, low-density lipoprotein.

At 6 months, HbA1c levels decreased to 8.5 [7.4–10.5] mmol/L in the DJBL group and 11.0 [9.3–13.1] mmol/L in the control group (P = 0.07). Fasting insulin levels were 15.0 [9.0–21.0] mU/L and 17.0 [13.0–36.0] mU/L in the DJBL and control groups, respectively (Table 1; P = 0.11). At month 12, mean body weight of the DJBL patients was still 6.8 [3.3–12.0] kg lower than at baseline. In the control group, the weight difference was 4.0 [0.8–8.6] kg compared with baseline (DJBL vs control; P = 0.07). Accordingly, at this time point, BMI was 2.2 [1.2–3.4] kg/m² lower than baseline in the DJBL group (P < 0.05). Importantly, DJBL patients still had an excess weight loss of 19.8% [10.6%–45.0%] versus 11.7% [1.4%–25.4%] in the control group (P < 0.05). The percent total weight loss was 5.8% [2.8%–11.1%] in the DJBL group versus 3.5% [0.6%–8.6%] in the control group (P < 0.05).

Effect of DJBL Versus Control Treatment on T2DM

At baseline, the DJBL group was characterized by an HbA1c level of 8.3% [7.7%–9.0%] versus 8.3% [7.7%–8.9%] in the control group (P = 0.82). The fasting glucose level was 11.0 [9.4–13.0] mmol/L in the DJBL group and 11.0 [9.3–13.1] mmol/L in the control group (P = 0.87). Fasting insulin levels were 15.0 [9.0–21.0] mU/L and 17.0 [13.0–36.0] mU/L in the DJBL and control groups, respectively (Table 1; P = 0.11). At month 12, mean body weight of the DJBL patients was still 6.8 [3.3–12.0] kg lower than at baseline. In the control group, the weight difference was 4.0 [0.8–8.6] kg compared with baseline (DJBL vs control; P = 0.07). Accordingly, at this time point, BMI was 2.2 [1.2–3.4] kg/m² lower than baseline in the DJBL group (P < 0.05).

Fasting glucose levels decreased to 11.1 [7.0–17.8] mU/L and 14.0 [10.0–19.8] mU/L in the DJBL and control groups, respectively (P = 0.40). In the DJBL group, 85.3% of the patients achieved a decrease in postprandial glucose excursion versus 48.7% in the control group (Figs. 4C, E; P < 0.05). In addition, changes in insulin levels as obtained during the meal tolerance tests are shown in Figures 4F–I.

At month 12, mean HbA1c levels increased to 7.3% [6.6%–8.0%] in the DJBL group versus an increase to 8.0% [6.8%–8.8%] in the control group (DJBL vs control; P = 0.95). Fasting glucose levels were 9.0 [7.4–11.1] mmol/L and 9.7 [8.4–12.3] mmol/L for the DJBL and control groups, respectively (P = 0.41), and fasting insulin levels were 15.0 [8.0–19.5] mU/L and 15.7 [8.6–23.6] mU/L, respectively (P = 0.73).
FIGURE 2. Illustration of the DJBL and the delivery system. A, DJBL. The device is endoscopically placed in the duodenum to form a barrier between chyme and the intestinal wall, mimicking the intestinal bypass component of the Roux-en-Y gastric bypass (B). C, The device comprises a 60-cm long impermeable fluoropolymer sleeve and a nitinol anchor with barbs. The polypropylene drawstring is necessary for removal of the device. D, The implant device with a guide wire, deployment device, and the encapsulated sleeve.

Changes in Glucose-Lowering Medication

All participants used glucose-lowering medication at baseline. In the DJBL group (n = 38), 36 patients were taking metformin, 28 patients were taking SU derivatives, and 17 patients were taking insulin. In the control group (n = 39), 33 patients were taking metformin, 30 patients were taking SU derivatives, and 19 patients were taking insulin.

Changes in glucose-lowering medication evaluated at month 6 and month 12 are displayed in Table 2. Importantly, the daily insulin dosage was more often decreased or discontinued in the DJBL group.
than in the control group (P < 0.05 at month 12). The same trend was observed for the usage of SU derivatives (P < 0.05 at month 12).

Effect of DJBL Versus Control Treatment on Cardiovascular Parameters

At baseline, 34% of the DJBL patients versus 41% of the diet patients were taking antihypertensive medication. During the course of the study, only minor medication changes were made. After 6 months of treatment, blood pressure decreased from 147 [139–156]/92 [82–96] mm Hg to 132 [122–140]/81 [72–90] mm Hg in the DJBL group and from 152 [138–160]/90 [82–96] mm Hg to 137 [124–148]/82 [79–90] mm Hg in the control group (Table 3; P = 0.25 for systolic blood pressure and P = 0.29 for diastolic blood pressure). Total cholesterol levels decreased from 4.4 [3.9–5.0] mmol/L to 3.7 [3.4–4.2] mmol/L in the DJBL group. In the control group, no change was observed: 4.4 [3.6–5.3] mmol/L versus 4.5 [3.9–5.1] mmol/L, DJBL versus control, respectively, at month 6 (P = 0.02).

At the end of the study, after 12 months, blood pressure had stabilized; for DJBL patients, the mean value was 130 [124–144]/82 [77–90] mm Hg versus 140 [122–148]/85 [78–90] mm Hg in the control group (P = 0.31 for systolic blood pressure and P = 0.38 for diastolic blood pressure). The total cholesterol level of all patients was comparable with baseline: 4.4 [4.0–5.3] versus 4.4 [3.9–5.1], DJBL versus control group, respectively (P = 0.79). Additional information on changes in high-density cholesterol, low-density cholesterol, and triglyceride levels is shown in Table 3.

Safety Data

In the DJBL group, 76.3% of the patients had at least 1 adverse event versus 59% of the patients in the control group. In the DJBL group, adverse events consisted mainly of minor GI complaints, abdominal pain, or discomfort (63.2% in the DJBL group vs 28.2% in the control group, respectively). In the DJBL group, these complaints occurred primarily during the early postimplant phase, within 2 weeks after the implantation. Complaints of nausea or vomiting occurred in 23.7% of the DJBL patients and in 17.9% of the control patients. The prevalence of hypoglycemic events was comparable between the 2 groups: 23.7% in the DJBL versus 25.6% in the control group.

In the DJBL group, there were 8 adverse events requiring hospitalization. Five of the 8 events were device related. One patient presented with melena and pain in the epigastric region; however, no bleeding was found during endoscopic evaluation and complaints disappeared with conservative treatment. An additional patient presented with abdominal discomfort and subsequent dehydration due to insufficient fluid intake, which was also managed conservatively. In 1 patient, the DJBL was blocked with food, making early removal

FIGURE 3. Effects of DJBL treatment versus control treatment on weight parameters. A, Weight changes over time for both the DJBL and the control group. B, The changes in BMI. C, The percentage of excess weight loss over time. D, The percentage of total body weight loss at all time points for both the DJBL and control group. *P < 0.05.
FIGURE 4. Effects of DJBL treatment type 2 diabetes parameters. A, The changes in plasma concentrations of HbA1c during the study period. B, Glucose concentrations of the DJBL group as obtained during the meal tolerance tests. C, The AUC calculations for glucose. D, The plasma glucose concentrations of the control group during the meal tolerance tests. E, The AUC calculations for glucose. F, Plasma insulin levels during the meal tolerance tests of the DJBL patients. G, For the DJBL group, the AUC calculations for insulin. H, The plasma insulin concentrations of the control patients as obtained during the meal tolerance tests. I, The AUC calculations for insulin. *P < 0.05. AUC indicates area under the curve.

necessary. One patient suffered from symptomatic gallstones during the course of the study and was treated with laparoscopic cholecystectomy. All device-related serious adverse events resolved without sequelae. Only one procedure-related serious adverse event occurred, an esophageal perforation during a scheduled DJBL removal at month 6. After an apparent uncomplicated removal, final endoscopic evaluation revealed a 6-cm longitudinal, partially transmural tear of the esophagus. This was probably caused by one of the barbs on the anchor that was not fully covered by the removal hood. Treatment of the perforation was performed by endoscopic stenting and placement of a feeding tube. After 3 weeks, the tear had resolved without sequelae and the patient completed the study. During the study, only one DJBL patient withdrew consent because of an adverse event of abdominal pain at day 10. Two additional patients were lost to follow-up (at days 191 and 272, respectively; for more information see Fig. 1).

In the control group, there were also 8 adverse events requiring hospitalization. By the end of the study, 5 events had resolved without sequelae. The events that did not resolve without sequelae consisted of myocardial infarction, humerus fracture, lower back hernia, diagnosis of cancer, and a nonspecified psychiatric disorder. In this group, 4 patients withdrew informed consent. One patient each at week 1, month 3, and day 315, and 1 patient withdrew consent at day 273 when received a diagnosis of cancer. One patient was lost to follow-up at day 267.

DISCUSSION

There is overwhelming evidence that bariatric surgery promotes weight loss and improves glucose homeostasis. Both Roux-en-Y gastric bypass and the biliopancreatic diversion seem to be the most effective procedures; both techniques cause significant weight loss and durable remission of T2DM. Interestingly, the improvement of T2DM occurs rapidly within days after both types of surgery. This rapid glycemic improvement is thought to be specifically attributable to the intestinal bypass component, which, according to the foregut hypothesis, results in glycemic improvement by reduced secretion of diabetogenic factors in the proximal small intestine. The hindgut hypothesis, on the contrary, attributes improved glycemic control to enhanced secretion of incretins in response
to undigested nutrients in the distal small intestine.\textsuperscript{27,30} Interestingly, exclusion of the proximal small intestine by means of the surgical duodenal-jejunal bypass, rapidly improves T2DM, even in nonobese patients.\textsuperscript{31}

The DJBL is a nonsurgical endoscopic device developed to create an intestinal bypass in a minimally invasive way.\textsuperscript{15,32} Previous studies have revealed positive effects of the DJBL on obesity, T2DM, and the metabolic syndrome.\textsuperscript{11–19} The aim of the current study was to investigate the effect of the DJBL on obesity and T2DM in a randomized manner, comparing 6 months of DJBL treatment in combination with dietary intervention with dietary treatment alone. This study is the first to report on 6 months of DJBL treatment compared with dietary intervention. Furthermore, our study included 6 months of post-DJBL removal follow-up.

Six months after treatment initiation, the DJBL group lost significantly more weight than the diet group. In addition, HbA\textsubscript{1c} levels decreased significantly compared with the control group. DJBL treatment was associated with a greater percentage of patients achieving a decrease in postprandial glucose levels. Furthermore, glucose-lowering medication was reduced or discontinued in more DJBL patients than in control patients. These results are in line with previous studies performed with the DJBL. Since the first report of a successful DJBL implant in a patient for a period of 3 months, resulting in a total weight loss of 9 kg,\textsuperscript{13} several studies have demonstrated positive effects of DJBL treatment on obesity.\textsuperscript{11,18} In addition, a marked improvement of T2DM was observed.\textsuperscript{11,15} Previously performed randomized controlled trials, comparing DJBL treatment versus sham or diet control treatment, have displayed superiority of the DJBL treatment and improvement of T2DM.\textsuperscript{12–15} Taken together, DJBL treatment in combination with a diet is more effective in treating obesity and T2DM than dietary intervention alone.

Interestingly, the mechanisms responsible for the effectiveness of duodenal-jejunal exclusion are still unknown. Because postprandial insulin secretion seemed stable over the course of the study, it is tempting to speculate that the rapid changes in the glucose response to a meal may result from increased insulin sensitivity and/or decreased hepatic glucose production.\textsuperscript{24} As previously shown, changes in glucagon-like peptide-1, glucose-dependent insulinnotropic polypeptide, and glucagon parallel this phenomenon.\textsuperscript{16}

Intraluminal implants in the digestive tract can theoretically be the cause of serious complications. Migration, bleeding, perforation, and obstruction are potential drawbacks and are reported often in numerous studies on stent placement for colonic malignancy.\textsuperscript{35} Although design, indication, and placement behind the pylorus of the DJBL are unprecedented, safety has been a point of meticulous observation. However, DJBL treatment for 6 months has shown to have a favorable risk/benefit ratio. In the current study, one procedure-related event occurred, requiring only conventional treatment. Moreover, the early removal rate was low (1/34) in this study. Adverse events were mild and most commonly consisted of abdominal discomfort and nausea. They typically occurred during the first few weeks after DJBL implantation and usually resolved without treatment and without sequelae. So far no mortality has been reported after DJBL treatment, with a published experience of around 300 patients worldwide. Therefore, the DJBL can be considered as a safe treatment option for obesity and T2DM.

After removal of the device, weight and HbA\textsubscript{1c} levels increased slightly in the DJBL group. A similar trend for weight and HbA\textsubscript{1c} levels was observed in the control group. At month 12, the percentage of excess weight loss and the percentage of total weight loss were still significantly greater in the DJBL group. Changes in weight and HbA\textsubscript{1c} levels were no longer statistically different between the groups. Importantly, weight and T2DM control remained improved compared with baseline in both groups. At the time of study initiation, the maximally approved DJBL treatment duration was 6 months in The Netherlands. de Moura et al\textsuperscript{17} were the first to investigate 1-year DJBL treatment and demonstrated the safety and efficacy of the DJBL in reducing obesity and T2DM on the longer term. These positive effects have now been confirmed by 2 additional 1-year prospective clinical studies.\textsuperscript{19,36} On the basis of these results, it might be expected that the improvement in T2DM observed in the current study with a treatment duration of 6 months would be even more pronounced with a longer treatment duration. As DJBL is an innovative technique, the maximum potential of this device is as yet uncertain. One of the drawbacks could theoretically be migration of the device’s anchor further into the duodenum. As the chance of migration potentially

### TABLE 2. Changes in Glucose-Lowering Medication

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Month 6</th>
<th>Month 12</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DJBL</td>
<td>Control</td>
</tr>
<tr>
<td>Metformin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased</td>
<td>8.8</td>
<td>7.7</td>
</tr>
<tr>
<td>Discontinued</td>
<td>2.9</td>
<td>—</td>
</tr>
<tr>
<td>Increased</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>SU derivatives</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased</td>
<td>47.1</td>
<td>38.5</td>
</tr>
<tr>
<td>Discontinued</td>
<td>14.7</td>
<td>23.1</td>
</tr>
<tr>
<td>Increased</td>
<td>2.9</td>
<td>2.6</td>
</tr>
<tr>
<td>Insulin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased</td>
<td>41.2</td>
<td>30.8</td>
</tr>
<tr>
<td>Discontinued</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Increased</td>
<td>—</td>
<td>10.3</td>
</tr>
</tbody>
</table>

The values given are percentages.

### TABLE 3. Changes in Blood Pressure and Cholesterol Profile

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Device Group</th>
<th>Diet Group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Month 6</td>
</tr>
<tr>
<td></td>
<td>Baseline</td>
<td>Month 6</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>4.4 [3.9–5.0]</td>
<td>3.7 [3.4–4.1]\textsuperscript{*}</td>
</tr>
<tr>
<td>HDL, mmol/L</td>
<td>1.1 [0.9–1.4]</td>
<td>1.0 [0.8–1.2]</td>
</tr>
<tr>
<td>LDL, mmol/L</td>
<td>2.3 [1.9–3.1]</td>
<td>2.0 [1.5–2.3]\textsuperscript{*}</td>
</tr>
<tr>
<td>Triglycerides, mmol/L</td>
<td>1.8 [1.3–3.3]</td>
<td>1.5 [1.2–2.0]</td>
</tr>
</tbody>
</table>

\textsuperscript{*}Data are given as mean [interquartile range] in mmol/L.

HDL indicates high-density lipoprotein; LDL, low-density lipoprotein.

Copyright © 2014 Lippincott Williams & Wilkins. Unauthorized reproduction of this article is prohibited.
increases when the device is left in place for a longer period of time, implantation time is extended only gradually in order not to compromise the patients’ safety. Next to longer implantation time, intermittent implantation could be a valid alternative to prolong the therapeutic effect of the DJBL and studies are now being conducted to evaluate the feasibility and efficacy of reimplantation.

With regard to cardiovascular risk profile, as already described by Cohen et al., subtle changes in cardiovascular risk profile can be of major clinical importance. In the current population, the 10-year risk for coronary heart disease according to the UK Prospective Diabetes Study Risk Engine would be, without intervention, approximately 14.0% in the DJBL group versus 12.5% in the control group at 12 months. With the DJBL intervention, the estimated 10-year coronary heart disease risk decreased by approximately 2% versus 1% decrease in the control group, possibly indicating superiority of the DJBL over dietary treatment with respect to reducing risk for development of cardiovascular disease.

In the treatment algorithm for obese patients with type 2 diabetes, the DJBL can be positioned in between medical therapy and invasive bariatric techniques. In addition, it might be beneficial to combine DJBL treatment with the very promising glucose-lowering therapies that have recently become available, such as glucagon-like peptide-1 agonists, dipeptidyl peptidase-4 inhibitors, and sodium/glucose cotransporter-2 inhibitors. In the current study, no patients using these types of medication were included; however, studies including these drugs seem of great interest.

CONCLUSIONS

The current data suggest that the DJBL is a valid alternative to invasive bariatric procedures in the treatment of obesity and T2DM. Six months of DJBL treatment plus dietary intervention leads to significant weight loss and improvement of T2DM compared with dietary treatment alone.

ACKNOWLEDGMENTS

The authors thank the patients contributing to this trial; the trial nurses Willemien Kuijper, Ivonne Wilts, and Rochele Niessen; the gastroenterologists Peter Wahab; Marcel Groeneweg, Rogier de Ridder, Ger Koek, and Minke Bakker for their help with the DJBL procedures; the endocrinologists Hans de Boer, Nicolaas Schaper, and Ruut Bianchi; researchers Edo Aarts and Freddye Verdam; statistician Aurora Liao and Anhngan Pham; LifeScan Inc, Milpitas, CA, for kindly providing One Touch Ultra glucometers and test strips; Stat Medical Devices Inc, North Miami Beach, FL, for kindly providing STAT-Lite Lacing Devices and STAT Comfort Thin Sterile Strips; Stat Medical Devices Inc, North Miami Beach, FL, for kindly providing STAT-Lite Lacing Devices and STAT Comfort Thin Sterile Strips; and the students who helped conducting this research. P. Koehestanie and C. de Jonge contributed equally to the manuscript. The authors contribution is as follows: The authors contributed in the following way: F.J.B., I.M.J., N.D.B., J.W.M.G.: study concept and design; P.K., C.d.J., F.J.B., I.M.J., N.D.B., J.W.M.G.: patient treatment; P.K., C.d.J.: collection of clinical samples; P.K., C.d.J.: acquisition of data; P.K., C.d.J., F.J.B., I.M.J., N.d.B., J.W.M.G.: analysis and interpretation of data; P.K., C.d.J.: drafting of the manuscript; All authors reviewed the manuscript for important intellectual content and accepted the manuscript.

REFERENCES


